REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 32, 36, 38, 40, 44, 46-51, 53-58, 62, 64, 65, 69, 71, 72, 74-77, 79 and 80 are currently pending. Claims 32, 38, 40, 44, 49, 65, 70 and 74 are amended herein. Independent claim 32 has been amended to recite the use of independent regulatory element to control expression of the recited papillomavirus polypeptides. Claims 40, 49, and 75 are amended herein to recite the structural features of the non-oncogenic variants. Claims 32, 33, and 65 have been amended to address issues of grammar. Claims 38 and 74 have been amended herein to recite proper antecedent basis. Per the above amendments, claims 50, 51, 57, 58, 76, and 77 are canceled herein as redundant.

Basis for these amendment may be found throughout the specification and claims as-filed, especially at page 11, line 6 the specification and in the examples, as well as in claims 50, 51, 57, 58, 76, and 77 as-filed. Thus, no new matter is introduced by way of this Amendment. Applicants reserve the right to file one or more continuation or divisional applications directed to ant subject matter canceled by way of this Amendment.

Claim Objections

Claims 32, 44 and 65 are objected to for the recitation of the phrase "vector into which are inserted" as this phrase is purportedly grammatically incorrect. Claims 32, 33,

and 65 have been amended to recite "vector into which is inserted". Thus, Applicants respectfully submit that the objections have been obviated.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 38 and 74 stand rejected under 35 U.S.C. 112, second paragraph, as purportedly indefinite. Claim 38 stands rejected for the recitation of the term "strain" as there is purportedly insufficient antecedent basis for this term in the claim. Claim 38 has been amended herein to replace the term "strain" with "vector", to provide antecedent basis.

Claim 74 stands rejected for the recitation of "recombinant vaccinia virus", "Copenhagen" and "strain" as there is insufficient antecedent basis for these limitations in the claim. Claim 74 has been amended herein to remove the recitation of the Copenhagen strain and to recite proper antecedent basis.

Thus, Applicants respectfully request that the rejections be withdrawn.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 40, 49 and 75 stand rejected under 35 U.S.C. 112, first paragraph, as purportedly failing to comply with the written description requirement.

The Office Action states that the specification has identified only one non-oncogenic species of E6 and E7, but that the claims do not require that the variants possess any particular distinguishing feature, biological activity, or conserved structure.

In the interest of expediting the present prosecution and without ceding to the outstanding rejection, claims 40, 49, and 75 are amended herein to recite the structural features of the non-oncogenic variants. Specifically, the claims as amended provide a composition wherein the E6 and/or E7 polypeptides are non-oncogenic variants of the native E6 and E7 polypeptides of a papillomavirus, wherein the non-oncogenic variant of the E6 polypeptide is the native HPV-16 E6 polypeptide deleted of amino acids 111-115, and wherein the nonocogenic variant of the E7 polypeptide is the native HPV-16 E7 polypeptide deleted of amino acids 21 to 26.

In light of the above amendments and remarks, Applicants request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 32, 36, 38, 53 and 54 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Lowy *et al.* (U.S. Patent No. 5,618,536), Hagensee *et al.* (*Journal of Virology*, 67(1): 315-322 (1993)), Borysiewicz *et al.* (*Lancet*, 347: 1523-1527 (1996)), Galloway (*Infectious Agents and Disease*, 3: 187-193 (1994)), and Meyer *et al.* (*Journal of General Virology*, 72: 1031-1038 (1991)).

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142.

Applicants respectfully submit that these criteria have not been met in the present Office Action.

Before turning to the cited references, Applicants note claim 32 is amended herein to recite DNA sequences under control of independent elements necessary for expression.

Lowy *et al.* disclose an anti-papillomavirus vaccine based on virus-like particles (VLPs). The VLPs are composed of capsidic antigens (L1, L2), and so may provide prophylactic protection against a subsequent infectious papillomavirus challenge. However, Lowy *et al.* fail to disclose or suggest an anti-papillomavirus composition based upon a MVA vector encoding the E6, E7, L1 and L2 polypeptides

To address the issue of therapeutic protection, Lowy *et al.* disclose chimeric VLPs having the papilloma E6 or E7 antigen incorporated into the viral capsid-like structure, such that the early antigen is exposed at the VLP surface. To this end, the L2 entity has been engineered as a fusion product with the E6 or E7 antigen. Example 1 of Lowy illustrates L2/E7 fusions involving two different strains of papillomaviruses (bovine BPV or human HPV16), two different E7 polypeptides (full length or N-terminal E7 residues 1-30) and two different fusion sites (C-terminus or between residues 274 and 275 of L2). The L2/E7 fusion is then cloned in a baculovirus comprising the wild-type L1 gene, and the chimeric VLPs are produced using a baculovirus vector. The chimeric LVPs are then injected into animal models in order to evaluate immunoprotection against HPV infection.

On page 6, the Office Action refers to claims 16 and 17 and column 4, line 62 to column 5, lines 2-9, stating that Lowy *et al.* disclose a DNA molecule directing the

expression of papillomavirus L1 and L2 polypeptides. However, in the passages cited by the Office Action, Lowy *et al.* leads the skilled artisan to believe that the DNA molecule is used as means to produce *in vitro* the therapeutics VLPs vaccine (*e.g.,* in mammalian, yeast or insect cells). Thus, Applicants submit that Lowy *et al.* fail to disclose or suggest an anti-papillomavirus composition based upon a MVA vector encoding the E6, E7, L1 and L2 polypeptides, as claimed in the present invention.

Furthermore, the presently claimed composition relies on the direct administration of a recombinant MVA vector that is capable of expressing the recited papillomavirus polypeptides, L1, L2, E6 and E7 antigens respectively, and producing them *in situ* within the treated patients. As illustrated in the working examples of the present specification, the claimed composition can be successfully used to prevent and treat HPV-induced tumors. In immunoprophylaxy experiments, mice vaccinated with the composition of the invention before tumor implantation show an important delay in tumor appearance. Moreover, one third of the challenged mice were still alive 51 days after the challenge whereas 100 percent of control animals died at day 36. Injection of the composition into animals that were pre-implanted with tumor cells expressing E6 and E7 papilloma genes leads to a significant protection resulting in marked increase in animal survival.

In contrast, Lowy *et al.* rely on chimeric L1, L2 and E7 papillomavirus polypeptides assembled in VLPs. In order to achieve therapeutic benefit, Lowy *et al.* disclose the presentation of the early polypeptide E7 at the surface of the VLPs, to be compatible with the immune effector cells. However, as illustrated by the working

examples of Lowy *et al.*, Applicants submit that this reference fails to provide any experimental data that could support effective therapeutic immunoprotection of the chimeric VLPs against HPV-induced tumors.

In fact, Lowy *et al.* demonstrate that the chimeric L2-E7 fusion is incorporated into the L1 based VLPs. The E7 moiety is indeed presented at the VLP surface since rabbits inoculated with such chimeric VLPs produce anti-E7 antibodies. However, apart from detecting neutralizing anti-E7 antibodies in immunized animals (humoral immunity) and demonstrating prophylactic protection against subsequent infections papillomavirus challenge, Lowy *et al.* fail to demonstrate the induction of a therapeutic protection provided the chimeric VLP particles presenting E7 at their surface, *i.e.*, a significant anti-tumor response. Example 13 of Lowy *et al.* merely describes the type of experimental procedures that could be used to evaluate a potential anti-tumoral efficacy, without any experimental results.

While, neutralizing antibodies may be useful in preventing infection, the cell-mediated immune response, and particularly those involving early papillomavirus antigens, it is also important in controlling regression of HPV infections. However, there is no disclosure or suggestion in Lowy *et al.* that the chimeric VLPs are capable of preserving the tri-dimentional structure of the E7 moiety when it is embedded into the viral capsid structure, and that the conformational epitopes which appear to be required for induction of therapeutically relevant immunity (CTL-mediated immunity) are indeed retained in chimeric VLPs.

Applicants submit that the vast majority of HPV-infected patients develop antibodies to the external L1 papillomavirus protein as they become infected (as disclosed in the secondary reference Galloway, on page 189). In this consideration, using chimeric VLPs for delivering E7 into an HPV-infected patient is likely to at least reduce the E7-mediated cell immune response, due to the risk of neutralization by pre-existing anti-L1 antibodies present in HPV-infected patients.

In the case of the present invention, based on the delivery of a MVA vector expressing the E6, E7, L1 and L2 papillomavirus antigens, the relevant papillomavirus polypeptides are produced *in situ*, and thus are not neutralized by pre-existing immunity immediately after injection. Moreover, expression of the individual late and early papillomavirus antigens from the MVA vector in their native form are more likely to preserve their tridimensional structure, and thus their natural presentation to the immune system, that we presume to be beneficial in terms of immunity.

The deficiencies of Lowy *et al.* with respect to the present invention are not remedied by the secondary references. The secondary references are addressed in detail below.

Hagensee *et al.* relate to the production of recombinant route of HPV-1 VLPs. This reference demonstrates that cells infected with a vaccinia virus encoding L1 and L2 (under the control of either the early 7.5K (pGS series) or a late (pMJ series) promoter produce capsids) are identical in appearance to the native HPV capsids, although production is more important when driven by the late promoter than by the 7.5K early promoter. As

mentioned on page 321 of Hagansee, the recombinant capsids will likely be important for academic studies with respect to HPV pathogenesis, packaging and assembly, and for further characterizing a host's immune response to HPV. Therefore, as before, Hagensee *et al.* relate to the use of VLP particles and not to a MVA-based composition.

Page 7 of the Office Action states that the skilled artisan would have been motivated to express the papillomavirus polypeptides of Lowy *et al.* in the vaccinia virus vector comprising the 7.5K promoter of Hengensee *et al.*, which permits to eliminate the time-consuming step of expressing and harvesting the recombinant polypeptides from cell culture. Applicants respectfully disagree.

The skilled artisan would not have been motivated to use the vaccinia virus system to express the papillomavirus polypeptides of Lowy *et al.*, in order to avoid an alleged cumbersome process for producing VLPs. There is no indication in the cited references that an alternative system should be developed to replace VLPs. Further, Hagensee *et al.* neither disclose nor even suggest expressing early papillomavirus antigens in addition to the L1 and L2, to provide additional therapeutic benefit against papillomavirus infections.

Finally, Applicants note that Lowy *et al.* disclose that E7-encoding sequences should be inserted within a late coding sequence in order to be amenable to the immune effector cells. Even if the skilled artisan were motivated to try the vaccinia virus vector comprising the 7.5K promoter described by Hagensee *et al.*, he would have expressed the L1 and L2/E7 fusion polypeptides to produce the chimeric VLPs in appropriate cell systems. Starting from Lowy *et al.* in combination with Hagensee *et al.*, the skilled artisan

would not have been motivated to express a vaccinia vector comprising the sequence encoding the two early antigens E6 and E7 placed under independent transcriptional and translational regulatory elements.

Boroysiewicz *et al.* disclose a recombinant vaccinia vector expressing the E6 and E7 polypeptides of HPV-16 and HPV-18 for immunotherapy purposes (TA-HPV). Three of the eight injected patients developed an HPV-specific response and therapeutic benefit was detected in one. However, Boroysiewicz *et al.* fail to suggest incorporating the late L1 and L2 polypeptides into the vaccinia virus encoding early papillomavirus polypeptides.

Galloway *et al.* is merely a review of human papillomavirus vaccines. Galloway *et al.* disclose prophylactic vaccination studies that have been performed with late papillomavirus polypeptides recombinantly produced as L1 and L2 fusion proteins, as well as therapeutic vaccination following administration of either E6 or E7-expressing fibroblasts or vaccinia virus recombinants expressing individual BPV E5, E6 or E7. The only composition combining early and late papillomavirus polypeptides disclosed in this document relies on a L2-E7 fusion protein (*see* pages 190-191).

Galloway *et al.* do not disclose a composition as claimed in the present invention comprising one MVA vector co-expressing L1, L2, E6 and E7 polypeptides under independent regulatory elements. The skilled artisan would not have been motivated to arrive at the present invention upon reviewing any of the cited references in combination with Galloway *et al.*, especially in view of the authors statement in the cited reference

indicating that it is unclear whether early and late HPV polypeptide combinations could provide effective protection or treatment against HPV-induced diseases. Moreover, Applicants note that the human clinical assays using an L2-E7 fusion protein (Cantab's TH-GW vaccine) were stopped due to its failure to demonstrate any therapeutic improvement over a placebo (*see* Antiviral Agents Bulletin Vol. 13).

Meyer *et al.* relate to MVA genome, and identify the six major deletions that have occurred during the attenuation process of the wild-type vaccinia strain. Meyer *et. al.* merely provides general knowledge about the MVA vector, but do not disclose or even suggest expressing HPV polypeptides and, optionally, immunostimulatory molecules as specified in the present claims. Further, Meyer *et al.* fails to disclose that 4 or even 5 different genes could be introduced in a single MVA vector and be expressed at sufficient levels to provide a therapeutic or a prophylactic benefit to an immunized organism against HPV infections and HPV-induced lesions. It is well known in the art that co-expression of two genes can be problematic. Thus, one of ordinary skill in the art would have no expectation of success in co-expressing of 4 or even 5 different genes in a single MVA vector.

Thus, in summary, the composition of the invention differs from that of Lowy *et al.* and the secondary references in several ways. Lowy *et al.* relate to a protein-based composition (made of virus-like particles) whereas the present invention relies on a vector-based composition. In addition, Lowy *et al.* disclose compositions combining L1, L2 and E7 polypeptides, wherein E7 is fused in frame to the L2 polypeptide, but fail to disclose a

vector co-expressing independently L1, L2, E6 as well as E7 polypeptides. Finally, Lowy *et al.* disclose that the E7 antigen should be presented at the surface of the VLP in order to elicit an effective humoral immunity (*i.e.*, generate antibodies directed against the fusion E7 partner). Hagensen *et al.* merely describe L1 and L2 production by recombinant techniques using vaccinia virus vectors. Boroysiewicz *et al.* merely describe a vaccinia virus vector expressing the early E6 and E7 papillomavirus antigens, for use in immunoprophylaxy. Galloway merely describes anti papillomavirus compositions comprising: a recombinant vector expressing (an) early papillomavirus polypeptide(s) to treat HPV infections, alate papillomavirus fusion polypeptide(s) to prevent HPV infections, or a E7+L2 fusion protein.

Finally, Meyer *et al.* merely describe the MVA genome.

The cited references, alone or in combination, would not have motivated one skilled in the art to use a single MVA vector co-expressing the recited papillomavirus genes under independent regulatory elements. Thus, claims 32, 36 and 38 are not obvious over the cited references.

Claims 40, 57 and 58 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Lowy *et al.*, Hagensee *et al.*, Borysiewicz *et al.*, Galloway, and Meyer *et al.* as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Crook *et al.* (*Cell*, 67: 547-556 (1991)) and Munger *et al.* (*EMBO Journal*, 8: 4099-4105 (1989)).

Lowy *et al.*, Hagensee *et al.*, Borysiewicz *et al.*, Galloway, and Meyer *et al.* as applied to claims 32, 36, 38, 53 and 54 are discussed above. Crook *et al.* disclose the residue of the E6 polypeptide involved in binding to p53. Amino acid delection of residues 111-115 in E6 reduces binding to p53. Munger *et al.* identify the residue of the E7 polypeptide necessary for complexing the retinoblastoma suppressor gene product (Rb). Amino acid deletion of residues 21-24 in E7 abolishes binding to Rb.

Without ceding to the Examiner's rejections, Applicants note that claim 32 is amended herein to recite DNA sequences being placed under the control of independent elements necessary for its expression in a host cell or organism. In light of this amendment and the remarks above regarding the cited references, Applicants request that this rejection be withdrawn.

Claims 44, 46, 48, 55, 56, 62 and 64 are rejected under 35 USC § 103(a), as allegedly unpatentable over Lowy *et al.* (U.S. Patent No. 5,618,536), Hagensee *et al.* (1993, *J. Virol.* 67:315-322), Boroysiewicz *et al.* (June 1996, *Lancet* 347:1523-7), Galloway (1994, *Infectious Agents and Disease* 3: 187-93) and Meyer *et al.* (1991, *J. Gen Virol.* 72:1031-8) as applied above, and further in view of Bubenik *et al.* (1996, *International J. Oncol.* 8:477-481).

Lowy *et al.*, Hagensee *et al.*, Borysiewicz *et al.*, Galloway, and Meyer *et al.* are discussed above. Bubenik *et al.* disclose a therapeutic method comprising the administration of HPV-16 infected tumor cells and repeated injection of recombinant IL-2.

The animals vaccinated with irradiated cells plus IL-2 in Bubenik *et al.* were protected to a greater extent than animals only treated with irradiated cells. Applicants note that the immunizing protocol described in the Material and Methods section of Bubenik *et al.* (*see* page 478), refers to the fact that experimental hamsters were immunized twice with irradiated HPV-16-induced tumor cells and injected in addition twice a day with a dose of $5x10^4$ i.u. of recombinant IL-2 for 5 days following each immunization (days 3-7 and 38-42). Thus, the immunized animals received a total of two doses of immunizing irradiated cells and twenty injections of recombinant IL-2 before being challenged with tumor cells on day 56.

Therefore, the method of the cited reference does not remedy the deficiencies of the primary reference. Bubenik *et al.* neither disclose nor suggest a composition as claimed based on the direct administration of MVA vectors encoding L1, L2, E6 and E7 papillomavirus polypeptides together with IL-2. Instead, the reference suggests a methodology wherein irradiated tumor cells are used. Applicants stress that the quantity of recombinant IL-2 that is used in Bubenik in order to obtain an adjuvanting effect is of note. Specifically, 20 injections of IL-2 doses (twice daily over two periods of 5 days) must be accomplished following the two injections of the vaccinating irradiated tumoral cells. Applicants draw the Examiner's attention to the fact that the Bubenik method would be far more difficult to implement for human cancer therapy than the gene transfer approach claimed in the present invention. In addition, due to the huge quantity of IL-2 that are necessary to augment the immune response to HPV-16 infected cells, Applicants submit

that the Bubenik *et al.* method fails to provide a reasonable expectation of success to one of ordinary skill in the art with respect to the direct administration of a MVA vector co-expressing papillomavirus antigens and IL-2 as claimed in the present application.

Claims 47 and 48 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Lowy *et al.* (U.S. Patent No. 5,618,536), Hagensee *et al.* (1993, *J. Virol.* 67:315-322), Boroysiewicz *et al.* (June 1996, *Lancet* 347:1523-7), Galloway (1994, *Infectious Agents and Disease* 3: 187-93) and Meyer *et al.* (1991, *J. Gen Virol.* 72:1031-8) as applied above, and further in view of Baltz (1995, *American Journal of Health-System Pharmacy*, 52-2574:2585) and Gajewski (1996, *The Journal of Immunology* 156:465-472).

The secondary references fail to remedy the deficiencies of the primary reference. Lowy *et al.*, Hagensee *et al.*, Borysiewicz *et al.*, Galloway, and Meyer *et al.* are discussed above. Baltz provides a general review on cancer immunology, discussing in very general terms the adjuvanting properties of a wide variety of molecules including cytokines such as B7.1. However, Baltz does not specifically disclose or suggest the claimed composition consisting of a MVA vector co-expressing E6, E7, L1 and L2 polypeptides and an immunostimulator such as B7.1. In particular, Batz fails to teach or suggest the combination of the late and early papillomavirus polypeptides and an immunostimulator.

Gajewski discloses the capacity of B7.1 to stimulate P815 specific CTL (*see* the abstract of the reference, reciting *"Thus, at least in the context of primary stimulation by irradiated P815 transfectants, B7.1 appears to be superior to B7.2 at co stimulation of*

CD8+ T lymphocytes.", and reciting at the end of the introduction section *"Thus, B7.1 but not B7.2 appears to be the preferred co stimulator molecule for CD8+ cells in the P815 tumor system.")*. Moreover, the enhancing effect is tested *in vitro* in combination with exogenous co-stimulatory molecules (such as IL-12 and IL-6 or low doses of anti-CD3 mAb). Based on these data, the skilled artisan would not have been motivated to incorporate the B7.1 gene into the papillomavirus expressing vector and to implement the direct administration of the MVA vector co-expressing these papillomavirus antigens together with B7.1 with a reasonable expectation of success.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Boroysiewicz *et al.* (June 1996, *Lancet* 347:1523-1527), Meyer *et al.* (1991, *J. Gen. Virol.* 72:1031-8) and Bubenik (1996, *International Journal of Oncology* 8:477-481).

Claims 75-77 stand rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Borysiewicz *et al.*, Meyer *et al.*, and Bubenik *et al.* as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook *et al.* and Munger *et al.* These references, and the reasons why they do not render the claimed invention unpatentable, are discussed in detail above.

As previously mentioned, Boroysiewicz *et al.* provides a lytic (Wyeth strain) vaccinia virus encoding both HPV016 and 18 E6/E7 fused proteins in head to head orientations under the control of p7.5 and H6 promoters. This reference does not describe

a composition as claimed consisting of one (non lytic) MVA vector expressing independently an immunostimulator together with the E6 or E7 polypeptides, especially one which would preserve the native conformation of the expressed HPV polypeptides, and thus benefit immunity. Applicants note that the vaccination studies performed by Boroysiewicz with the E6/E7 fusion-expressing vaccinia virus demonstrate a humoral response in 3 out of 8 treated patients, *i.e.*, induction of anti-HPV18 E7 antibodies, and a CTL response in one patient after boosting with an adenovirus vector. However, antitumor effectiveness of the Boroysiewicz's composition could not be determined. As discussed previously, the secondary references do not remedy the deficiencies of Boroysiewicz.

In the light of the above comments and claim amendments, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: December 1, 2003

By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620